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Original article

Correlation between Serum Estrogen Level and Endometrial Histology in Cases of Fibroid Uterus in Peri-menopausal Period

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Abstract

Background: Uterine leiomyoma represents over 75% of the amiable tumours in ladies of conceptive age amass. Endometrium is a hormonally responsive tissue. The reaction of endometrium to incitement by endogenous or exogenous steroid hormones is unsurprising endogenous reaction is an impression of the hypothalamic–pituitary-ovarian pathway. **Aim of this study:** to assess serum level of E2 and study endometrial histological changes in instances of fibroid uterus. **Patients and methods:** This study included forty ladies have symptomatic fibroid uterus. history was taken, general examination, ultrasound examination, measuring serum estradiol and endometrial biopsy was taken by D&C or hysterectomy sent for histopathological examination. **Results:** endometrial thickness was >10mm in 69.2% of premenopausal and >5mm in 83%of postmenopausal. endometrial hyperplasia is the commonest glandular endometrial change represent (37.5%), complex hyperplasia without atypia 5%, simple hyperplasia with atypia 5% and proliferative endometrium 22.5%of all review bunch. in premenopausal patients hyperplasia with atypia related with the most elevated E2 level (252,6 pg) , complex hyperplasia without atypia with E2 level (221.6 ±6.22 SD), hyperplasia without atypia with E2 level (184.84 ± 12,11SD) and in postmenopausal patients hyperplasia with atypia with E2 level (245.3 pg), hyperplasia without atypia (145.68 ±33.53 SD) .**Conclusion** : there is correlation between serum oestrogen level , histopathological changes of endometrium and symptomatic fibroid uterus at perimenopausal age .

Key words: Estrogen, Endometrial histology, Fibroid, Peri-menopausal.

Introduction

Uterine leiomyomas represent over 75% of the considerate tumors in ladies of regenerative age gather. [(1)]

Uterine fibroids or leiomyoma are benign tumour of the uterine muscle, called myometrium. They contain receptors for female conceptive hormones (estrogen and progesterone) and other compound receptors identified with estrogen generation (aromatase receptors). At the point when the receptors are available in the fibroid, the development of the fibroid will be fortified by these hormones. The reason for leiomyoma advancement is not completely comprehended. **(2)**

The study of disease transmission of the most widely recognized purpose behind hysterectomy, fibroids, is pretty much obscure. It has been assessed that 30% of ladies would have fibroids after their 40th birthday. In the United States uterine fibroids are among the five most incessant indicative gynecologic gatherings as per late insights. Most elevated rates for fibroids in the US were among ladies 40–44 years old. [(3)]

Endometrium is a hormonally delicate and responsive tissue of the body. The reaction of endometrium to endogenous or exogenous steroid hormones is an unsurprising endogenous reaction is an impression of the hypothalamic–pituitary-ovarian hub. Comprehension of the perplexing cooperation of this connection between these structures is vital. **(4)**

Unopposed estrogens for treating menopausal manifestations were broadly utilized when epidemiological discoveries related them with an expanded endometrial growth hazard. Including progestogens switch this reaction effectively yet understanding, dosage, sort and particularly time amid which the progestogen is regulated are critical. [(5)]

A wide range of regimens are presently accessible utilizing oral, transdermal, subcutaneous, intravaginal or intra uterine use of the estrogen as well as progestogen. **(6)**

Menorrhagia is for the most part acknowledged by gynecologists as generally because of the nearness of fibroids, particularly submucous. Myomectomy eases menorrhagia in most ladies with fibroids and is particularly viable when a solitary sub mucous fibroid is expelled hysteroscopically. In any case, the menorrhagia related with fibroids is likewise alleviated by endometrial resection and there are narrative reports that the levonorgestrel discharging intrauterine framework is comparably compelling. **(7)**

Aim of the work: This study intended to assess serum level of E2 and study endometrial histological changes in instances of fibroid uterus.

Patients and methods

This was prospective study included 40 patients with fibroid uterus The study was done at Benha university Hospitals during the period from June 2023 to January 2024.

Ethical approval was obtained from the local ethical committee of Benha Faculty of medicine with REC (RC 33-5-2023).

Informed written consent from each case was obtained after Explanation of the procedures, investigations, side effects of this study and they had the chance to participate or not.

Inclusion criteria: All cases analysed by ultrasound to have symptomatic fibroid uterus conceded for endometrial biopsy or hysterectomy.

Exclusion criteria:

- Cases in which irregular bleeding is not of uterine source.
- Cases with systemic reasons for uterine bleeding as, coagulation defect or infection.
- Cases who deny endometrial biopsy or surgical management.
- Cases with additional uterine pathology.

Methods:

- Complete history taking and examination.
- Routine investigations as CBC and liver and kidney functions tests.
- Measuring serum estrogen level.
- Pelvic ultrasound examination.
- Endometrial biopsy and histopathological examination.

Statistical methods : Data were entered, checked and analyzed using SPSS v26 (IBM Inc., Armonk, NY, USA) for Windows version 8.

Results

The study included 40 cases every one of them have fibroid uterus. The age of the cases extend from 40-60 yrs. with mean age 47,75 with± 7,16 SD 90% of patients were in age (40-60) however under 40 years of age was in 10% of patients, no statistically significant difference between premenopausal and postmenopausal according to demographic data **Table (1)**. There was no statistically significant difference between premenopausal and postmenopausal according to bleeding and by chance there were three cases complaining of stress incontinence and there was one case in premenopausal group and one case in postmenopausal group has more than one complains. There was statistically significant difference between premenopausal and postmenopausal according location of fibroid and there was one case in premenopausal group and one case in postmenopausal group has multiple fibroids in different locations. There was statistically significant difference between premenopausal and postmenopausal in estradiol E2 level and endometrial thickness that was higher in premenopausal group **Table (2)**. no statistically significant difference between premenopausal and postmenopausal according to endometrial histopathological findings. **Table (3).** There was a statistically highly significance relation between serum estradiol level and endometrial changes in premenopausal group **Table (4)**. There was a statistically highly significance relation between serum estradiol level and endometrial histopathological findings in postmenopausal group **Table (4).** There was Significant relation between

endometrial thickness ≥10 and histopathological findings with estradiol E2 in premenopausal **Table (5)**. There is a statistically significant relation between endometrium thickness and histopathological findings with estradiol E2 in postmenopausal. **Table (5)**.

Table (1): Comparison between premenopausal and postmenopausal group according demographic data.

Demographic Data	**Premenopausal**		**Postmenopausal**		**Chi-square test**	
	No.	**%**	**No.**	**%**	**x2**	**p-value**
Age	30-60 [47.75±7.16]					
Range [Mean±SD]						
Parity						
Nullipara	2	12.5	2	8.3	5.016	0.414
Multipara	13	81.3	17	70.8		
Grandmultipara	1	6.2	5	20.9		
BMI [kg/(m)^2]						
Normal (18.5-24.9)	11	68.8	20	83.3	1.402	0.496
Overweight (25-29.9)	2	12.5	1	4.2		
Obese (30-35)	3	18.8	3	12.5		

Table (2): Comparison between premenopausal and postmenopausal group according Estradiol E2 level (pg/ml) and endometrial thickness (mm). .

Estradiol E2 level (pg/ml)	**Premenopausal**	**postmenopausal**	**t-test**	**p-value**
Mean±SD	131.74±76.83	89.91±70.24	3.160	**0.035 (S)**
Range	35.70-252.60	4.00-245.30		
Thickness (mm)	**Premenopausal**	**Postmenopausal**	**t-test**	**p-value**
Mean±SD	9.06±2.82	7.65±4.11	1.441	0.237
Range	3-12	2.0-14.0		

Table (3): Comparison between premenopausal and postmenopausal group according to endometrial histopathological findings.

Changes	Premenopausal		Postmenopausal		Chi-square test	
	No.	%	No.	%	x2	p-value
Dilated distorted glands	5	31.3	3	12.5	7.882	0.163
Senile cystic atrophy	0	0.0	4	16.7		
Simple hyperplasia without atypia	5	31.3	10	41.7		
Complex hyperplasia without atypia	2	12.5	0	0.0		
Simple hyperplasia with atypia	1	6.3	1	4.2		
Proliferative endometrium	3	18.8	6	25.0		
Total	16	100.0	24	100.0		

Table (4): Relation between endometrial histopathological finding and estradiol E2 level (pg/ml) in premenopausal group and postmenopausal group .

Changes in Premenopausal group	Estradiol E2 level (pg/ml)		t-test	
	Mean	±SD	T	p-value
Dilated distorted glands	63.62	14.03	66.323	**<0.001 (HS)**
Simple hyperplasia without atypia	184.84	12.11		
Complex hyperplasia without atypia	221.60	6.22		
Simple hyperplasia with atypia	252.60	0.00		
Proliferative endometrium	56.57	32.49		
Changes in Postmenopausal group	**Estradiol E2 level (pg/ml)**		**t-test**	
	Mean	**±SD**	**T**	**p-value**
Dilated distorted glands	71.63	17.80	39.379	**<0.001 (HS)**
Senile cystic atrophy	8.30	3.29		
Simple hyperplasia without atypia	145.68	33.53		
Simple hyperplasia with atypia	245.30	0.00		
Proliferative endometrium	34.60	16.92		

Table (5): Relation between endometrial thickness and endometrial histopathological findings with Estradiol E2 in premenopausal and postmenopausal group.

Thickness (mm)	Changes	Estradiol E2 level (pg/ml) ≤158		>158		Chi-square test	
		No.	%	No.	%	x2	p-value
<5	Dilated distorted glands	1	12.5%	0	0.0%	-	-
	Proliferative endometrium	1	12.5%	0	0.0%		
5- <10	Dilated distorted glands	2	25.0%	0	0.0%	-	-
	Proliferative endometrium	2	25.0%	0	0.0%		
>=10	Dilated distorted glands	2	25.0%	0	0.0%	10.000	0.019
	Simple hyperplasia without atypia	0	0.0%	5	62.5%		
	Complex hyperplasia without atypia	0	0.0%	2	25.0%		
	Simple hyperplasia with atypia	0	0.0%	1	12.5%		

Relation between endometrial thickness and endometrial histopathological findings with Estradiol E2 in postmenopausal group

Thickness (mm)	Changes	Estradiol E2 level (pg/ml) ≤54		>54		Chi-square test	
		No.	%	No.	%	x2	p-value
<5	Dilated distorted glands	1	10%	2	14.2%	5.143	0.076
	Senile cystic atrophy	2	20%	0	0.0%		
	Proliferative endometrium	4	40%	0	0.0%		
5- <10	Senile cystic atrophy	2	20%	0	0.0%	1.333	0.248
	Proliferative endometrium	1	10%	1	7.1%		
>=10	Simple hyperplasia without atypia	0	0.0%	10	71.5%	-	0.017
	Simple hyperplasia with atypia	0	0.0%	1	7.1%		

Discussion

Uterine leiomyoma, or fibroids, are the most widely recognized tumor of the female pelvis. The general frequency is in the vicinity of 4% and 11%, however it ascends to about 40% in ladies beyond 50 years old. [8]

In the present study most of the patients were multiparous (90%). This outcome agrees with that performed before that indicated that 82% of fibroid cases were multiparous while just 18% were nullipara. [9]

On the other hand, it found that parous women had lower risk of UL than nulliparous women (HR 0.40; 95% CI 0.30–0.53). [10]

In the present study, unusual uterine bleeding was most normally connected with submucosal and intramural fibroids with a recurrence of 71.4% and 61.6% individually. This result agrees with others, who demonstrated that anomalous uterine draining for the

most part basic related with submucous sort 68.4% and intramural by 60% [11].

Endometrial pathology demonstrated that simple hyperplasia without atypia 37.5%, proliferative endometrium 22.5%, dilated distorted glands 20%, senile cystic atrophy 10%, complex hyperplasia without atypia 5% and hyperplasia with atypia 5% and in the same line, in a study done in 2016, microscopic examination of endometrium revealed 50.7% cases of proliferative phase and 22.7% cases of endometrial hyperplasia. Endometrial stromal changes noted were hemorrhage, chronic endometritis, and tubercular endometritis Dual pathology of leiomyoma and adenomyosis was noted in 29.1% [12].

In the current study endometrial thickness in postmenopausal was (7.65± 4.11) mm which must be under 5 mm however in premenopausal was (9.06 ± 2.8) mm. There was a relation between endometrial thickness with serum estradiol and endometrial change, in premenopausal and postmenopausal cases. This agreed with the results which proved that the mean of serum estradiol level of follicular stage is <158 pg/ml in premenopausal women, while mean of serum estradiol level in postmenopausal ladies is<54 pg/ml. [13]

Other investigators demonstrated that the impact of estradiol on endometrium changes, by giving 0.625-1.25mg/dl ethinyl estradiol once per day for 12 months and measurement of serum estradiol level outcome indicated high plasma level. Then the researchers took endometrial biopsy, the pathology result demonstrate that all cases create endometrial hyperplasia, because of impact of long presentation to estradiol. [14]

In patients with postmenopausal bleeding and fibroid uterus, serum estradiol levels are fundamentally higher contrasted with that of sound postmenopausal ladies. This finding substantiates the reality that progressions of endogenous estrogen levels have huge effect on proliferative changes of the postmenopausal endometrium. Constant unopposed estrogen introduction to the endometrium brings about endometrial hyperplasia, besides, endometrial carcinoma may build up, This study in concurrence with investigation of others [15] that indicated hyperplasia with atypia found with estradiol level 205,8 pg/ml followed by hyperplasia without atypia found with estradiol level 133,6 pg/ml in post-menopausal cases. [15]

This study was not without limitations. Limited power of the study and other ethnicities need to be distributed well in further studies. The notable strength of the study was confirmation of the effect of unopposed estradiol exposure on endometrium and its relation to histopathological changes.

Conclusion

There is correlation between serum oestrogen level, histopathological changes of endometrium and symptomatic fibroid uterus at peri-menopausal age.

References

1-Giuliani E, As-Sanie S, Marsh EE. Epidemiology and management of uterine fibroids. Int J Gynaecol Obstet. 2020 Apr;149(1):3-9. doi: 10.1002/ijgo.13102. Epub 2020 Feb 17. PMID: 31960950.

2- Wise LA, Laughlin-Tommaso SK. Epidemiology of uterine fibroids: from menarche to menopause. Clin Obstet Gynecol. 2016;59(1):2-24.

3- Cheng LC, Li HY, Gong QQ, Huang CY, Zhang C. regional, and national burden of uterine fibroids in the last 30 years: Estimates from the 1990 to 2019 Global Burden of Disease Study. Front Med (Lausanne). 2022 Nov 7;9:1003605. doi: 10.3389/fmed.2022.1003605. PMID: 36419793; PMCID: PMC9676237.

4- Williams AR, Bergeron C, Barlow DH, Ferenczy A. Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. Int J Gynecol Pathol. 2012 Nov;31(6):556-69. doi: 10.1097/PGP.0b013e318251035b. PMID: 23018219.

5 -Tsigkou A, Reis FM, Lee MH, Jiang B, Tosti C, Centini G, et al.. Increased progesterone receptor expression in uterine leiomyoma: correlation with age, number of leiomyomas, and clinical symptoms. Fertil Steril. 2015 Jul; 104(1):170-5.e1. doi: 10.1016/j.fertnstert.2015.04.024. Epub 2015 May 23. PMID: 26006736.

6-Hackethal A, Brüggmann D, Leis A, Langde S, Stillger R, Münstedt K. Surgical management of uterine fibroids in Hesse, Germany, between 1998 and 2004. Fertil Steril. 2009 Mar;91(3):862-8. doi: 10.1016/j.fertnstert.2007.12.016. Epub 2008 Mar 4. PMID: 18304546.

7-Munro MG. Uterine leiomyomas, current concepts: pathogenesis, impact on reproductive health, and medical, procedural, and surgical management. Obstet Gynecol Clin North Am. 2011 Dec;38(4):703-31. doi: 10.1016/j.ogc.2011.09.006. PMID: 22134018.

8-Barjon K, Mikhail LN. Uterine Leiomyomata. [Updated 2023 Aug 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK546680/

9-Terry KL, De Vivo I, Hankinson SE, Missmer SA. Reproductive characteristics and risk of uterine leiomyomata. Fertil Steril. 2010 Dec;94(7):2703-7. doi: 10.1016/j.fertnstert.2010.04.065. Epub 2010 Jun 8. PMID: 20627243; PMCID: PMC2956020.

10- Song S, Park S, Song BM, Lee JE, Cha C, Park HY. Risk of uterine leiomyomata with menstrual and reproductive factors in premenopausal women: Korea nurses' health study. BMC Womens Health. 2023 Jun 9;23(1):305. doi: 10.1186/s12905-023-02447-4. PMID: 37296433; PMCID: PMC10257256.

11- Puri K, Famuyide AO, Erwin PJ, Stewart EA, Laughlin-Tommaso SK. Submucosal fibroids and the relation to heavy menstrual bleeding and anemia. Am J Obstet Gynecol. 2014 Jan;210(1):38.e1-7. doi: 10.1016/j.ajog.2013.09.038. Epub 2013 Sep 28. PMID: 24080304; PMCID: PMC4142474.

12-Geethamala K, Murthy VS, Vani BR, Rao S. Uterine Leiomyomas: An ENIGMA. J Midlife Health. 2016 Jan-Mar;7(1):22-7. doi: 10.4103/0976-7800.179170. PMID: 27134477; PMCID: PMC4832891.

13-Wong JY, Gold EB, Johnson WO, Lee JS. Circulating Sex Hormones and Risk of Uterine Fibroids: Study of Women's Health Across the Nation (SWAN). J Clin Endocrinol Metab. 2016 Jan;101(1):123-30.

doi: 10.1210/jc.2015-2935. Epub 2015 Dec 15. PMID: 26670127; PMCID: PMC4701845.

14-Genant HK, Lucas J, Weiss S, Akin M, Emkey R,. Low-dose esterified estrogen therapy: effects on bone, plasma estradiol concentrations, endometrium, and lipid levels. Estratab/Osteoporosis Study Group. Arch Intern Med. 1997 Dec 8-22;157(22):2609-15. doi: 10.1001/archinte.157.22.2609. PMID: 9531230.

15-Furness S, Roberts H, Marjoribanks J, Lethaby A, Hickey M,. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD000402. doi: 10.1002/14651858.CD000402.pub3. Update in: Cochrane Database Syst Rev. 2012;8:CD000402. PMID: 19370558.

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